

Statistical Analysis Plan

COMETA Study

COMETA study carried out for Janssen México

Innoval study coordinator

Janssen, México,

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Version 1.0

General

This document describes the tasks that form part of the statistical analysis to be carried out by Innoval S.A. de C.V. for the COMETA study, approved by Janssen México (hereinafter Janssen)

Background

We have established that sixty patients will form the basis of comparing the effect of four weeks' daily treatment with canagliflozin and sitagliptin by measuring the change in the level of glucose. The sample size was estimated for an ongoing response variable of compared study patient pairs.

The study is a multi-center, 2 x 2 randomized, double blind, crossed, actively controlled study on Diabetes Mellitus 2 patients whose glucose is not properly controlled, using stable doses of metformin (MET) monotherapy (1,500 mg/day) as oral treatment once a day, plus canagliflozin 300 mg or the dipeptidyl peptidase-4 inhibitor (DPP-4); stable doses of sitagliptin phosphate 100 mg once a day for 28 days, with a for sixteen-day washout period with MET monotherapy. Therefore, the interval between the first and last dose of adjuvant treatment is 72 days. With a pre-study interval of sixteen days (optional pre-selection period of six days; selection lasting three days; selection lasting seven days) and a post-treatment monitoring period of up to nine days. The maximum duration of the study for each patient who tolerates the drug and who does not withdraw his or her consent is, therefore, 97 days. A window of ± 3 days was taken into account for each of these visits, so that individual patients could be programmed. Patients are randomized double blind to treatment, the period and the sequence.

Objectives of the study.

The main objective of the study is to compare four weeks of treatment with CANA 300 mg with SITA 100 mg as a complement to metformin at a stable dose on glycemic

variability (GV), measured using continuous glucose measurements (CGM), when each drug is added to MET treatment, in stable doses in patients receiving type 2 DM treatment (T2DM) whose glucose is not properly controlled with MET monotherapy. The measurement of the primary efficacy result is the coefficient of variation of the CV intra-patient mean (SD)/fasting plasma glucose (FPG) mean.

Other study objectives include comparisons between the effect that this adjuvant treatment has on the following changes from the baseline:

1. Mean 24-hour glucose level (mg/dL).
2. Mean pre-prandial glucose (SD) [fasting plasma glucose (FPG)].
3. Mean two-hour postprandial glucose (PPG) (SD).
4. Time, percentage of time or AUC24h (or AOC24h for hypoglycemia) with glucose in euglycemic, hyperglycemic and hypoglycemic ranges.

Statistical analysis plan.

To make sure that the data gathering protocol is adhered to, Janssen will set up a clinical monitoring procedure so that certain action may be to deal with any problem that may arise regarding any missing or doubtful data, by means of a data enquiry process.

Following are the stages of the statistical analysis process:

1. Once Janssen has completed the data enquiry process, it must notify Innoval accordingly so that it may close the database and begin the statistical data analysis.
2. Innoval will carry out an exploratory data analysis in three weeks, consisting of the following stages:

Week one

- a. Data encoding. A list will be drawn up that specifies all variables of the electronic patient case report form (eCRF), their characteristics and the parameter range assigned to each answer given on the eCRF.
- b. Data compiled from the sample will be organized and ordered according to the type of variable and type of measurement, whether quantitative (numerical) or qualitative (nominal or categorical).

Weeks two and three

- a. Patient information will be summarized and specified according to the type of variable, using the descriptive data analysis.
 - i. Frequencies and percentages (tables and graphs) will be analyzed for nominal and categorical variables.
 - ii. Summary methods will be used for quantitative variables (numerical data): central trend measurements (mean and median); dispersion measurements (interquartile range, deviation and range) and position measurements (percentiles and quartiles).

b. Assessment of analysis of study groups and attributes of interest.

i. **Patients whose glucose is not properly controlled during the screening visit.**

The number of patients that meet this criterion will be established. The numerical HbA1c variable of the eCRF will be assessed as a categorical value:

Category	Hemoglobin values (HbA1C)
Glucose not properly controlled	7.5 to 10.5%
Glucose properly controlled	≤ 7.4%
Glucose not properly controlled, more than 10.5% of HbA1C)	> 10.6%

ii. **Stable dose of metformin.** The number of patients who meet this criterion will be established. Numerical variable metformin: Doses per day will be assessed as a categorical variable:

Category	Dose of metformin mg/day
Patients with a stable dose of metformin	≥ 1,500 mg/day
Patients without a stable dose of metformin	> 1,500 mg/day

iii. **Body mass index by tercile according to sex.** The number of patients who meet this criterion will be established. The numerical BMI variable will be assessed as a categorical variable:

Tercile Category	BMI men (kg/m ²)	BMI women (kg/m ²)
Tercile 1	22 to <28	22 to <30
Tercile 2	28 to <33	30 to <36

Tercile 3	33 to <45	36 to <45
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- iv. **Glucose in the euglycemic, hyperglycemic and hypoglycemic ranges.** The numerical variables with glucose values are: *Glucose (serum chemistry Panel* visit 1 and visit 13), *CGM Report* (visits 4, 8 and 12), *Glucometer* (visits 4, 8 and y 12) will be assessed as a variable. IMPORTANT: the ranges and parameters for these ranges are not specified in the protocol.

2. The above analysis will form the basis of a meeting to be held between Janssen and Innoval at which Innoval will submit the findings of its exploratory analysis, such as:

- a. Missing data,
- b. Possible unusual distribution patterns
- c. Potential extreme values that may affect distribution of the variable of interest.
- d. Based on the results of the exploratory analysis submitted, Janssen will establish:
 - i. Additional associations of variables that reflect results desired.
 - ii. Confirmation of multi-varied analysis (proposed on point 6).
 - iii. Possible alternative analyses.

3. After the meeting, analysis agreements will be documented.

4. Janssen must confirm and approve the analyses that Innoval will carry out in the final statistical analysis.

5. As soon as Janssen gives its confirmation and approval, Innoval carry out a final statistical data analysis in two weeks.

If the exploratory analysis does not come up with values that may influence distribution of the variable of interest, objectives will be assessed as follows:

Weeks four and five

- a. The primary objective will be assessed in terms of efficacy using:

i. **Glucose values** *CGM Report (interstitial glucose)*. Visit 4 (Baseline), Visit 8 (*First Treatment*) and Visit 12 (*Second treatment*) obtained during a period of six months after each active treatment.

ii. **Glucose variable values** *Glucometer (plasma glucose)*. Visit 4 (Baseline), Visit 8 (**First Treatment**) and Visit 12 (**Second treatment**) obtained during a period of six months after each active treatment.

The mean change of these variables will be assessed (standard deviation) with regard to the baseline point using the intra-patient variation coefficient of glucose profiles, calculated as follows: $(DS/\text{mean glucose} \times 100)$.

b. The same variables as those above will be used to assess secondary efficacy objectives, the only difference being that normality will be assessed using the Shapiro-Wilk test. The value of the mean (standard deviation) will be presented for normally distributed data and the median and interquartile range will be presented for data not distributed normally.

i. Average value (mean or median) of 24-hour glucose levels (mg/dL).

ii. Average value (mean or median) and standard deviation or interquartile range of pre-prandial glucose (mg/dL) (fasting plasma glucose) and two-hour postprandial glucose (PPG)).

iii. Time and percentage of time or AUC_{24h} or (AOC_{24h} for hypoglycemia).

1. Time (minutes), percentage of 24 hours or area under the glucose curve – time of 24 hours (AUC_{24h}) with glucose = 70–139 mg/dL (time elapsed with PG within the reference range).

2. Time (minutes), percentage of 24 hours or area under the glucose curve – time of 24 hours (AUC_{24h}) with glucose = 70–180 mg/dL (time elapsed with PG within the reference range).

3. Time (minutes), percentage of 24 hours or AUC_{24h} (mg/dL/h) with glucose >140 mg/dL (time elapsed with PG above reference range).

4. Time (minutes), percentage of 24 hours or AUC_{24h} (mg/dL/h) with glucose >180 mg/dL (time elapsed with PG substantially above reference range).

5. Time (minutes), percentage of 24 hours or area above the PG curve – time of 24 hours (AOC24h; mg/dL/h) with glucose <70 mg/dL.

c. The paired exact Fisher test will be used for all other differences between treatments that Janssen wants to be assessed for categorical baseline variables and paired t tests or Wilcoxon tests for ongoing efficacy assessment criteria distributed normally and abnormally (respectively), according to the results of the Shapiro-Wilk test. All other tests will be carried out using a bilateral α bilateral value = 0.05 (in other words, an a priori signification level of $p < 0.05$).

6. Once this has been done, Innoval will submit the following documents:

- a. A final statistical analysis.
- b. Original database.
- c. Encoded database.
- d. Working database and carrying out of statistical analysis.

END OF DOCUMENT.

Document approval

Date FELIX RODRIGUEZ GUTIERREZ <div style="text-align: center;"> Signature Maria Félix Rodriguez Gutierrez Associate Director- Global Trial Manager </div>	Date PATRICIA CABRERA JARAMILLO <div style="text-align: center;"> Signature Patricia Cabrera Regional Medical Director </div>
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Date	<div style="text-align: center;"> Signature Salvador Duran Coyote Clinical Research and Scientific Analysis Manager </div>
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